Variation in genes and hormones of the hypothalamic-pituitary-ovarian axis in female mood disorders - A systematic review and meta-analysis

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Review article

Variation in genes and hormones of the hypothalamic-pituitary-ovarian axis in female mood disorders – A systematic review and *meta*-analysis

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ABSTRACT

Women's increased risk for depression during reproductive transitions suggests an involvement of the hypothalamic-pituitary-ovarian (HPO) axis. This is the first systematic review and *meta*-analysis of HPO functioning in female mood disorders. Inclusionary criteria were: i) women suffering from premenstrual dysphoric disorder (PMDD) or a depressive disorder, ii) assessment of HPO-axis related biomarkers, iii) a case-control design. Sixty-three studies (N = 5,129) were included. There was evidence for PMDD to be paralleled by lower luteal oestradiol levels. Women with depression unrelated to reproductive transition showed lower testosterone levels than healthy controls and there was some evidence for lower dehydroepiandrosterone sulfate levels. There were no differences in HPO-related parameters between women with pregnancy, postpartum, and perimenopausal depression and controls. Women with PMDD and depression unrelated to reproductive transitions exhibit specific changes in the HPO-axis, which potentially contribute to their symptoms. Further research into reproductive mood disorders characterised by extreme endocrine changes is warranted.

1. Introduction

It has long been known that women have a twofold increased lifetime risk of suffering from depressive disorders compared to men (Kessler and Bromet, 2013). Although psychosocial factors clearly contribute to this, accumulating evidence also suggests hormonal influences.

Given that menarche is linked to an elevated risk for a first-onset depressive disorder (Soares and Zitek, 2008), a likely involved system is the hypothalamic-pituitary-ovarian (HPO) axis. Among other functions, follicle-stimulating hormone (FSH) and luteinising hormone (LH) act at the ovaries to stimulate the production of steroid hormones, such as oestradiol and progesterone (Burger et al., 2004). These steroid hormones are potent neuromodulators affecting brain regions involved in mood and behaviour (Toren et al., 1996). Similarly, allopregnanolone (ALLO), testosterone, and dehydroepiandrosterone (DHEA) have been implicated in mood and cognition (Toren et al., 1996; Bäckström et al., 2014; Pluchino et al., 2015). In human pregnancy, particularly, a progressive increase in placental production of corticotropin-releasing hormone (CRH), adenocorticotropic hormone (ACTH), estrogens and progesterone are observed, followed by an abrupt drop at delivery and reaching pregravid levels in the initial postpartum days (Economides et al., 1987; Speroff and Fritz, 2005). In line with these findings, hormonal alterations during the luteal phase (De Ronchi et al., 2005), pregnancy and postpartum period (Brummelte and Galea, 2010), and perimenopause (Schmidt and Rubinow, 2009) have been shown to be involved in the pathogenesis of female depressive disorders.

Indeed, various reproductive transition phase mood disorders have been described in the literature. Premenstrual dysphoric disorder (PMDD) is characterised by a variety of affective and somatic changes occurring during the luteal phase of the menstrual cycle; pregnancy and postpartum depressive disorders (PPD) present core symptoms comparable to major depression, with a distinctive onset around childbirth; perimenopausal depressive disorder involves mood symptoms and other complaints prevailing during the menopausal transition (Studd and Nappi, 2012). Notably, however, (major) depressive disorders, which are among the most prevalent and debilitating mental disorders, can occur throughout the lifespan and are not necessarily tied to reproductive events (Kennedy and Eisfeld, 1999).

In order to investigate to what extent the HPO axis is involved in various female mood disorders, we conducted the first systematic review and *meta*-analysis comparing women with and without reproductive transition phase mood disorders as well as women with and without

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depressive disorders unrelated to reproductive transition phases regarding HPO-axis-related parameters.

2. Methods

2.1. Search

Records were initially identified as part of a larger PubMed and PsycInfo search from the first available year until November 2018 (Fischer et al., 2019). This search was repeated to include all papers until September 2020. Key words and subject headings were chosen in accordance with the thesaurus of each database. A two-component search string was used: 1) "depressive disorder", including synonyms and 2) "HPO axis", including synonyms and components (e.g., "oestradiol"; see Table 1). A human filter was applied and only studies published in English, German, Dutch, French, Italian, Portuguese or Spanish were considered. A manual review of reference lists was conducted to identify additional studies. We sought for summary estimate data.

2.2. Screening

The following inclusion criteria were used: 1) adult women suffering from PMDD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) (APA, 2013) or any depressive disorder according to the DSM, the International Classification of Diseases (ICD) (WHO, 1992), Research Diagnostic Criteria (RDC) (Spitzer et al., 1978), or, for depression in pregnancy and PPD, the use of the Edinburgh Postnatal Depression Scale (Cox et al., 1996) including validated cut-off scores for the country where the study was conducted, 2) assessment of FSH, LH, oestradiol, progesterone, allopregnanolone, testosterone, DHEA, or DHEA sulfate (DHEA-S) or related genes, and 3) a case-control design. Studies on bipolar disorder were excluded unless results were reported separately for unipolar and bipolar depression; the same applied to studies including men. Studies in which hormonal medications were allowed were excluded, unless results for an unmedicated group were reported. Besides pregnancy and early postpartum studies, if hormone intake was not mentioned as an exclusion criterion, studies were excluded. Studies accepting use of antidepressants without separately reporting results for unmedicated patients were excluded. Comorbidity as well as intake of medication other than hormones or psychotropic drugs were allowed, but recorded for subgroup analyses/*meta*-regressions. The screening was conducted by two of the study investigators (RAC and SF) and disagreements were discussed until consensus was reached.

2.3. Data extraction

For each study, information about the sample size, ethnicity, diagnostic procedures, eligibility criteria, HPO-axis assessment, and relevant results were collected. Risk of bias was evaluated using a quality assessment scale adapted from previous *meta*-analyses (Fischer et al., 2019; Tak et al., 2011) (see Supplement Tables 1–4). Five items were scored on a 3-point scale (0–2). Data extraction was conducted by two of the study investigators (RAC and SF) and the risk of bias was assessed by two of the study investigators (UE and SF) and a research assistant.

2.4. Data analysis

Standardised mean differences (SMD) were calculated based on means or medians and standard deviations, standard errors, or ranges. Whenever insufficient information was reported, the study authors were contacted. Studies whose authors were unable to provide the necessary statistical data were included in the systematic review. Hedges' *g* was calculated to correct for small sample bias and studies were weighed and integrated based on their inverse variance (Borenstein et al., 2009). Random-effects *meta*-analyses were computed using Review Manager

Table 1
Search Terms.

PubMed	PsycINFO
Hypothalamic-pituitary-gonadal axis	**Hypothalamic-pituitary-gonadal axis**
A4	A4
A5	A5
androgen	androgen
Androgens as MeSH	Androgens as DE
androst*	androst*
dehydroepiandrosterone	dehydroepiandrosterone
DHEA	DHEA
DHT	DHT
dihydrotestosterone	dihydrotestosterone
E2	E2
E3	E3
E4	E4
ERα	ERα
ERβ	ERβ
ERS1	ERS1
ERS2	ERS2
estetrol	estetrol
estradiol	estradiol
estriol	estriol
estrogen*	estrogen*
Estrogens as MeSH	Estrogens as DE
Follicle Stimulating Hormone as MeSH	Follicle Stimulating Hormone as DE
"follicle-stimulating hormone"	"follicle-stimulating hormone"
FSH	FSH
gestagen*	gestagen*
Gestagen as MeSH	
"gonadal hormone"	"gonadal hormone"
"gonadal hormones"	"gonadal hormones"
"gonadal steroid"	"gonadal steroid"
"gonadal steroid hormones"	
"gonadal steroids"	"gonadal steroids"
"gonadal axis"	"gonadal axis"
gonadotropin*	Gonadotrophic Hormones as DE
Gonadotropins as MeSH	gonadotropin*
GPER	GPER
GPR30	GPR30
"hypothalamic-pituitary-gonadal axis"	"hypothalamic-pituitary-gonadal axis"
"hypothalamic-pituitary-ovarian axis"	"hypothalamic-pituitary-ovarian axis"
LH	LH
Luteinizing Hormone as MeSH	Luteinizing Hormone as DE
"luteinising hormone"	"luteinising hormone"
"luteinizing hormone"	"luteinizing hormone"
NR3A1	NR3A1
NR3A2	NR3A2
NR3C3	NR3C3
NR3C4	NR3C4
oestetrol	oestetrol
oestradiol	oestradiol
oestriol	oestriol
oestrogen	oestrogen
progestagen*	progestagen*
progestogen*	progestogen*
progesterone	progesterone
Progesterone as MeSH	Progesterone as DE
P4	P4
"sex hormone"	"sex hormone"
"sex hormones"	"sex hormones"
"sex steroid"	"sex steroid"
"sex steroids"	"sex steroids"
SHBG	SHBG
testosterone	testosterone
Depressive disorders	**Depressive disorders**
"affective disorder"	"affective disorder"
"affective disorders"	"affective disorders"
Affective Disorders as MeSH	Affective Disorders as DE
depress*	depress*
dysthymi*	dysthymi*
MDD	MDD
MDE	MDE
"mood disorder"	"mood disorder"
Mood Disorders as MeSH	"mood disorders"

(*continued on next page*)

Table 1 (*continued*)

PubMed	PsycINFO
PMDD	PMDD
PMS	PMS
"postpartum blues"	"postpartum blues"
"premenstrual dysphoric disorder"	"premenstrual dysphoric disorder"
Premenstrual Dysphoric Disorder as MeSH	Premenstrual Dysphoric Disorder as DE
"premenstrual syndrome"	"premenstrual syndrome"
Premenstrual Syndrome as MeSH	Premenstrual Syndrome as DE
"premenstrual symptoms"	"premenstrual symptoms"

(RevMan) Version 5.3 (Higgins and Green, 2011). Forest plots were also created with RevMan. Separate analyses were conducted for each HPO-axis parameter and, for PMDD, for each menstrual cycle phase. Heterogeneity was estimated using I^2 and X^2 statistics. Subgroup analyses and random-effects *meta*-regressions were undertaken to study potential effect modifiers (https://mason.gmu.edu/~dwilsonb/ma.html). This included all subitems of the quality assessment scales, sampling tissue (blood vs. saliva), as well as menstrual cycle phase (for PMDD) and menopausal status (for depressive disorders unrelated to reproductive transition phases). When menopausal status was not appropriately described, we inferred it based on the participants' mean age. Funnel plots, Egger's regression test and a trim-and-fill procedure were used to examine publication bias if more than ten studies were available.

3. Results

3.1. General study characteristics

The study selection is summarised in Fig. 1 and the study characteristics are presented in Tables 2–5. Sixty-three studies were included (PMDD = 33, pregnancy and PPD = 8, perimenopausal depressive disorder = 5, depressive disorders unrelated to reproductive transition phases = 17), comprising N = 5,129 women. The studies were published between 1981 and 2019. Sample sizes varied from 10 to 713. Age ranged from 18 to 85 years. Regarding HPO-axis assessments, 44.5% of the included studies measured parameters in serum, 28.7% used plasma, 7.9% blood (not further specified), 4.8% saliva, 3.1% urine, and 7.9% both serum and plasma, while 3.1% did not reveal information on tissue.

3.2. Premenstrual dysphoric disorder

Thirty-three studies compared women with PMDD and healthy controls regarding HPO-related parameters. Four of these were likely to

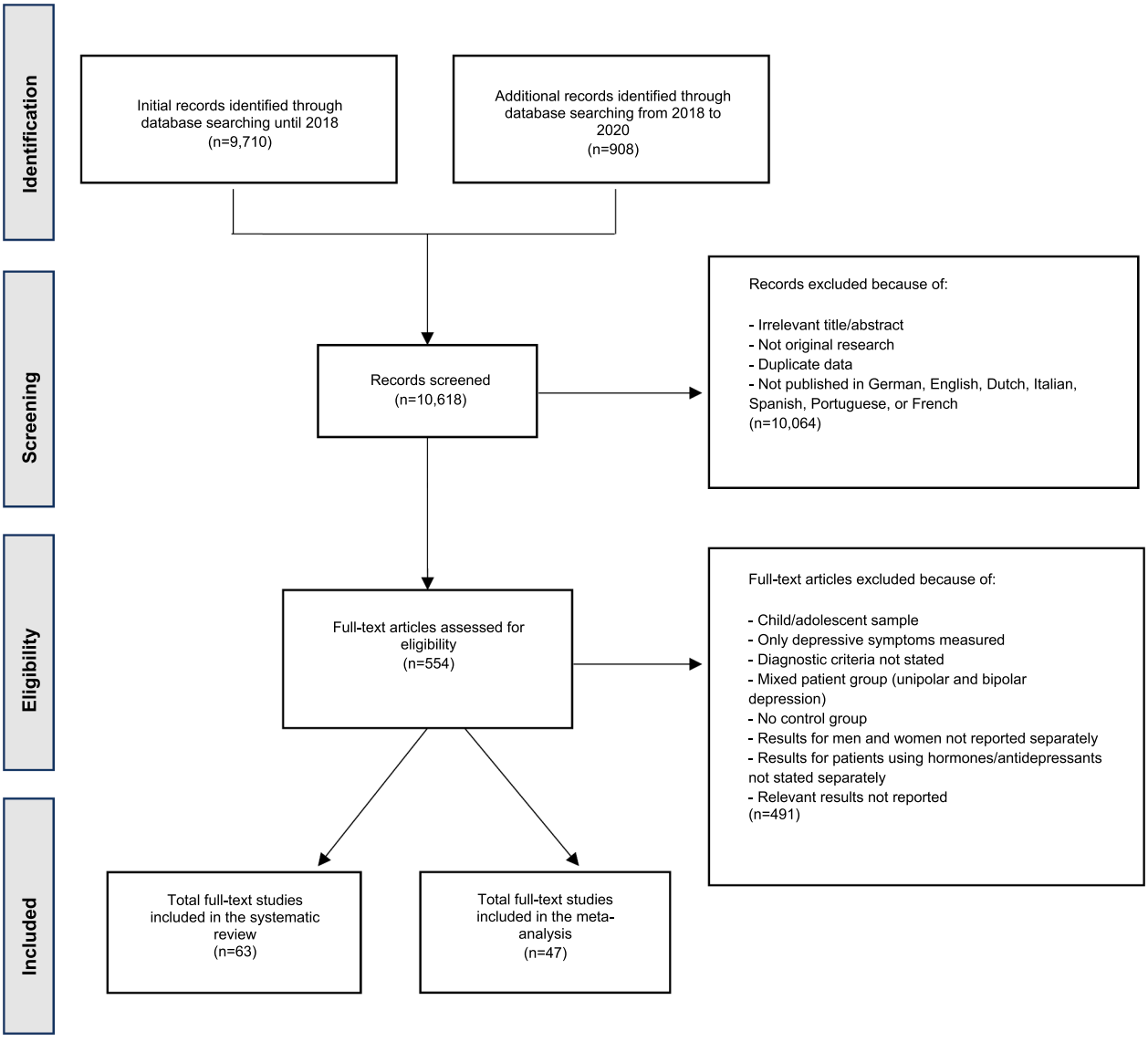

Fig. 1. Study selection.

Table 2
Characteristics of studies investigating hormones of the hypothalamic-pituitary-ovarian axis in premenstrual dysphoric disorder.

Study	N (total)	Cases	Controls	Measurement time points	Tissue	Hormones	Quality rating
Rubinow et al., 1988	N = 26	n = 17	n = 9	Follicular and luteal phase	Plasma	FSH LH Oestradiol Progesterone Testosterone DHEA-S	5
Eriksson et al., 1992	N = 22	n = 11	n = 11	Follicular phase, ovulation, luteal phase	Serum	Progesterone Testosterone DHEA DHEA-S	5
Cerin et al., 1993	N = 47	n = 27	n = 20	Follicular and luteal phase	Serum	Oestradiol Progesterone	6
Dennerstein et al., 1993	N = 83	n = 65	n = 18	Follicular phase, ovulation, luteal phase	Urine	Oestrogen	4
Rapkin et al., 1996	N = 12	n = 6	n = 6	Luteal phase	Serum	LH Oestradiol Progesterone	6
Wang et al., 1996	N = 20	n = 12	n = 8	Follicular and luteal phase	Plasma/serum	LH Oestradiol Progesterone	2
Rapkin et al., 1997	N = 71	n = 35	n = 36	Luteal phase	Serum	Progesterone Allopregnanolone	6
Bloch et al., 1998	N = 20	n = 10	n = 10	Follicular phase, ovulation, luteal phase	Plasma	Testosterone	5
Rapkin et al., 1998	N = 64	n = 32	n = 32	Luteal phase	Serum	Oestradiol Progesterone	6
Sundström et al., 1998	N = 24	n = 12	n = 12	Follicular and luteal phase	Plasma	Oestradiol Progesterone	4
Sundström et al., 1999	N = 14	n = 7	n = 7	Follicular and luteal phase	Plasma	Oestradiol Progesterone	2
Parry et al., 2000	N = 30	n = 15	n = 15	Follicular and luteal phase	NI	FSH LH Oestradiol Progesterone	6
Girdler et al., 2001	N = 36	n = 24	n = 12	Follicular and luteal phase	Plasma/serum	Progesterone Allopregnanolone	7
Roca et al., 2003	N = 14	n = 6	n = 8	Follicular and luteal phase	Plasma	Oestradiol Progesterone Testosterone	7
Jovanovic et al., 2006	N = 10	n = 5	n = 5	Follicular and luteal phase	Plasma	FSH LH Oestradiol Progesterone	2
Klatzkin et al., 2006	N = 52	n = 23	n = 29	Luteal phase	Plasma/serum	Progesterone Allopregnanolone	6
Thys-Jacobs et al., 2008	N = 115	n = 68	n = 47	Follicular phase, ovulation, luteal phase	Serum	LH Oestradiol Progesterone	7
Kask et al., 2009	N = 28	n = 16	n = 12	Luteal phase	Plasma	Oestradiol Progesterone	1
Rapkin et al., 2011	N = 24	n = 12	n = 12	Follicular and luteal phase	Plasma	Oestradiol Progesterone	5
Gingnell et al., 2012	N = 29	n = 14	n = 15	Follicular and luteal phase	Serum	Oestradiol Progesterone	2
Shechter et al., 2012	N = 10	n = 5	n = 5	Follicular and luteal phase	Plasma	Oestradiol Progesterone	3
Akturk et al., 2013	N = 38	n = 20	n = 18	Follicular and luteal phase	Serum	Progesterone	5
Gingnell et al., 2013	N = 28	n = 14	n = 14	Follicular and luteal phase	Serum	Oestradiol Progesterone	3
(Segebladh et al., 2013)	N = 56	n = 26	n = 30	Luteal phase	Serum	Allopregnanolone	5
Ko et al., 2014	N = 142	n = 67	n = 75	Follicular and luteal phase	Serum	Oestrogen Progesterone	4
Bartley et al., 2015	N = 28	n = 14	n = 14	Follicular phase, ovulation, luteal phase	Saliva	Oestradiol Progesterone Testosterone	6
Oral et al., 2015	N = 49	n = 20	n = 29	Follicular and luteal phase	Serum	Oestradiol Progesterone	7
(Eriksson et al., 2016)	N = 20	n = 12	n = 8	Follicular and luteal phase	Plasma	Oestradiol Progesterone	4
Timby et al., 2016	N = 20	n = 10	n = 10	Follicular and luteal phase	Serum	Allopregnanolone	5
Ozcan et al., 2017	N = 50	n = 20	n = 30	Follicular and luteal phase	Serum	Oestrogen Progesterone	6
Yen et al., 2018	N = 196	n = 100	n = 96	Follicular and luteal phase	Serum	Oestrogen	4
Yen et al., 2019	N = 116	n = 63	n = 53	Luteal phase	Serum	FSH LH Oestrogen Progesterone	5

Notes: DHEA = dehydroepiandrosterone, DHEA-S = dehydroepiandrosterone sulphate, FSH = follicle-stimulating hormone, LH = luteinising hormone, NI = not indicated.

Table 3
Characteristics of studies investigating hormones of the hypothalamic-pituitary-ovarian axis in pregnancy and postpartum depressive disorder.

Study	N (total)	Cases	Controls	Measurement time points	Tissue	Hormones	Quality rating
Harris et al., 1989	N = 147	n = 32	n = 115	6–8 weeks postpartum	Plasma	Oestradiol Progesterone	2
Harris et al., 1996	N = 120	N = 7	N = 113	At baseline, and 1, 5 and 35 days postpartum	Plasma	Oestradiol Progesterone	2
Klier et al., 2007	N = 89	n = 12	n = 70	1 and 3 days postpartum	Plasma/ serum	Oestradiol Progesterone	6
Chatzicharalampous et al., 2011	N = 57	NI	NI	Upon admission for delivery and daily until 4 days postpartum	Serum	Oestradiol Progesterone Testosterone	3
Posadas et al., 2012	N = 33	n = 11	n = 22	At approximately 30 weeks gestation	Serum	Oestradiol Progesterone	7
Saleh et al., 2013	N = 120	n = 60	n = 60	7 days postpartum	Serum	Oestradiol	4

Note: NI = not indicated.

Table 4
Characteristics of studies investigating hormones of the hypothalamic-pituitary-ovarian axis in perimenopausal depressive disorder.

Study	N (total)	Cases	Controls	Measurement time points	Tissue	Hormones	Quality rating
Schmidt et al., 2002	N = 92	n = 47	N = 45	At least six months of irregular menstrual cycles, but no more than 12 months of amenorrhoea	Plasma	FSH LH Oestradiol Testosterone DHEA DHEA-S	5
Flores-Ramos et al., 2014	N = 63	n = 44	n = 19	Perimenopause according to STRAW criteria	Serum	FSH LH Oestradiol Progesterone	4
Karaoulanis et al., 2014	N = 48	n = 22	n = 26	Irregular menstrual cycles or amenorrhoea for less than 12 months	Serum	FSH LH Oestradiol	4
Gordon et al., 2016	N = 19	n = 9	n = 10	Perimenopause according to STRAW criteria	Saliva	Oestradiol	4
Hui et al., 2016	N = 64	n = 38	n = 26	Perimenopause according to STRAW criteria	Serum	Oestradiol Testosterone	5

Note: DHEA = dehydroepiandrosterone, DHEA-S = dehydroepiandrosterone sulphate, FSH = follicle-stimulating hormone, LH = luteinising hormone, STRAW = Stages of Reproductive Aging Workshop.

have some participant overlap (Gingnell et al., 2013, 2012; Rapkin et al., 1997, 1998). For the hormonal studies, the average score of the quality assessments was 4.7 (see Table 2).

3.2.1. Genetic studies

One study investigated SNPs within oestrogen receptor genes (*ESR1*, *ESR2*). The authors found the genotype and allele frequencies of four SNPs (rs3020314, rs3003917, rs3020377, rs1884051) within *ESR1* to significantly differ between Caucasian women with PMDD and controls (Burger et al., 2004). No significant differences emerged regarding *ESR2*.

3.2.2. Hormonal studies

3.2.2.1. Follicle-stimulating hormone. Three studies assessed FSH in the follicular phase, whereas four assessed it in the luteal phase (Jovanovic et al., 2006; Rubinow et al., 1988; Parry et al., 2000; Yen et al., 2019). Insufficient data were available for a *meta*-analysis in the follicular phase, but *meta*-analysis in the luteal phase exhibited a null-finding (k = 2; $g = 0.07$, 95 %CI [−0.28, 0.42]; Z = 0.39, $p = .70$; $I^2 = 0\%$).

3.2.2.2. Luteinising hormone. Four studies measured LH in the follicular phase (Jovanovic et al., 2006; Rubinow et al., 1988; Parry et al., 2000; Wang et al., 1996). *Meta*-analysis revealed no differences between cases and controls (k = 2; $g = 0.17$, 95 %CI [−0.72, 1.06]; Z = 0.38, $p = .70$). Seven studies measured LH in the luteal phase; again, *meta*-analysis revealed a null-finding (k = 4; $g = -0.12$, 95 %CI [−0.36, 0.13]; Z = 0.93, $p = .35$; $I^2 = 0\%$) (Jovanovic et al., 2006; Rubinow et al., 1988; Parry et al., 2000; Yen et al., 2019; Wang et al., 1996; Thys-Jacobs et al., 2008; Rapkin et al., 1996).

3.2.2.3. Oestradiol. Nineteen studies measured oestradiol in the follicular phase (Gingnell et al., 2013, 2012; Jovanovic et al., 2006; Rubinow et al., 1988; Parry et al., 2000; Wang et al., 1996; Rapkin et al., 2011; Shechter et al., 2012; Ko et al., 2014; Bartley et al., 2015; Oral et al., 2015; Ozcan et al., 2017; Eriksson et al., 2016; Roca et al., 2003; Sundström et al., 1998, 1999; Dennerstein et al., 1993; Cerin et al., 1993; Yen et al., 2018). *Meta*-analysis yielded no group differences (k = 16; $g = -0.08$, 95 %CI [−0.25, 0.10]; Z = 0.87, $p = .39$; $I^2 = 15\%$; $\chi^2 = 17.68$, df = 15, $p = .28$; see also Fig. 2). Three studies assessed oestradiol in the ovulation phase (Thys-Jacobs et al., 2008; Bartley et al., 2015; Dennerstein et al., 1993) and *meta*-analysis yielded a non-significant result (k = 3; $g = -0.11$, 95 %CI [−0.67, 0.45]; Z = 0.37, $p = .71$; $I^2 = 70\%$). Twenty-four studies measured oestradiol in the luteal phase (Gingnell et al., 2013, 2012; Rapkin et al., 1998; Jovanovic et al., 2006; Rubinow et al., 1988; Parry et al., 2000; Yen et al., 2019; Wang et al., 1996; Thys-Jacobs et al., 2008; Rapkin et al., 2011; Shechter et al., 2012;

Table 5
Characteristics of studies investigating hormones of the hypothalamic-pituitary-ovarian axis in depressive disorder unrelated to reproductive transition phases.

Study	N (total)	Cases	Controls	Measurement time points	Tissue	Hormones	Quality rating
Amsterdam et al., 1981	N = 38	n = 19	n = 19	Premenopause, follicular phase	Plasma/ serum	FSH LH Oestradiol Testosterone	3
Winokur et al., 1982	N = 26	n = 14	n = 12	Premenopause	Plasma/ serum	FSH LH	2
Amsterdam et al., 1983	N = 27	n = 18	n = 9	Postmenopause	Plasma/ serum	FSH LH Oestradiol	3
Young et al., 2000	N = 24	n = 12	n = 12	Premenopause	Plasma	FSH LH Oestradiol Progesterone	4
Antonijevic et al., 2003	N = 35	n = 16	n = 19	Premenopause, follicular phase, and postmenopause	Plasma	FSH LH Oestradiol	4
Rajewska and Rybakowski, 2003	N = 90	n = 60	n = 30	Premenopause, follicular phase	Blood	FSH Oestradiol	2
Erdinçler et al., 2004	N = 87	n = 34	n = 53	NI	Plasma	Oestradiol Progesterone Testosterone DHEA-S	4
Poór et al., 2004	N = 32	n = 11	n = 21	NI	Urine	DHEA	2
Markianos et al., 2007	N = 118	n = 43	n = 75	Premenopause and postmenopause	Plasma/ serum	Testosterone DHEA-S	2
Oulis et al., 2014	N = 103	n = 38	n = 65	Premenopause and postmenopause	Plasma	Testosterone DHEA-S	4
(Kumsar et al., 2014)	N = 82	n = 52	n = 30	Premenopause, follicular phase	Serum	Testosterone	6
Findikli et al., 2017	N = 58	n = 34	n = 24	Premenopause	Serum	Oestradiol	3
Jiang et al., 2017	N = 37	n = 18	n = 19	Premenopause, follicular phase	Saliva	DHEA DHEA-S	8
Özdemir et al., 2017	N = 107	n = 58	n = 49	NI	Serum	Testosterone	3

Note: DHEA = dehydroepiandrosterone, DHEA-S = dehydroepiandrosterone sulfate, FSH = follicle-stimulating hormone, LH = luteinising hormone.

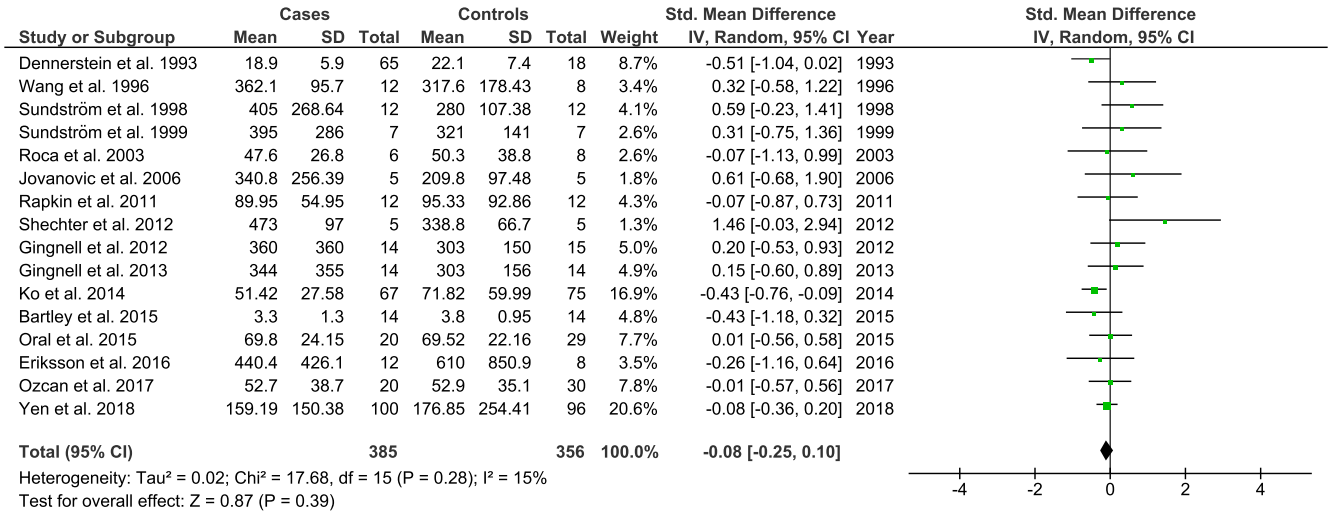

Fig. 2. Forest plot of studies comparing oestradiol in the follicular phase between women with premenstrual dysphoric disorder (PMDD) and healthy controls; negative effect sizes indicate that women with PMDD had lower oestradiol levels than controls.

Ko et al., 2014; Bartley et al., 2015; Oral et al., 2015; Ozcan et al., 2017; Eriksson et al., 2016; Roca et al., 2003; Sundström et al., 1998, 1999; Dennerstein et al., 1993; Cerin et al., 1993; Yen et al., 2018; Kask et al., 2009; Rapkin et al., 1996). While *meta*-analysis was non-significant (k = 21; $g = -0.09$, 95 %CI [−0.29, 0.11]; Z = 0.90, $p = .37$; see also Fig. 3), heterogeneity was significant ($I^2 = 51\%$; $\chi^2 = 41.20$, df = 20, $p = .004$). A subgroup analysis of *late* luteal phase studies did not alter the null-finding. However, *meta*-regression revealed that studies standardising their hormonal measures regarding time of day found lower oestradiol in individuals with PMDD than in healthy controls ($\beta = -0.37$, $p = .044$; k = 7; $g = -0.35$, 95 %CI [−0.57, −0.13]; Z = 3.12, $p = .002$; $I^2 = 0\%$).

3.2.2.4. Progesterone. Twenty-one studies measured progesterone in the follicular phase (Gingnell et al., 2013, 2012; Jovanovic et al., 2006; Rubinow et al., 1988; Parry et al., 2000; Wang et al., 1996; Thys-Jacobs et al., 2008; Rapkin et al., 2011; Shechter et al., 2012; Ko et al., 2014; Bartley et al., 2015; Oral et al., 2015; Ozcan et al., 2017; Eriksson et al., 2016; Roca et al., 2003; Sundström et al., 1998, 1999; Cerin et al., 1993; Yen et al., 2018; Akturk et al., 2013; Eriksson et al., 1992). No significant differences emerged between cases and controls (k = 16; $g = -0.19$, 95 %CI [−0.42, 0.03]; Z = 1.68, $p = .09$; $I^2 = 32\%$; $\chi^2 = 21.98$, df = 15, $p = .11$; see also Fig. 4). Three studies measured progesterone in the ovulation phase. *Meta*-analysis yielded a null-finding (k = 2; $g = 0.08$;

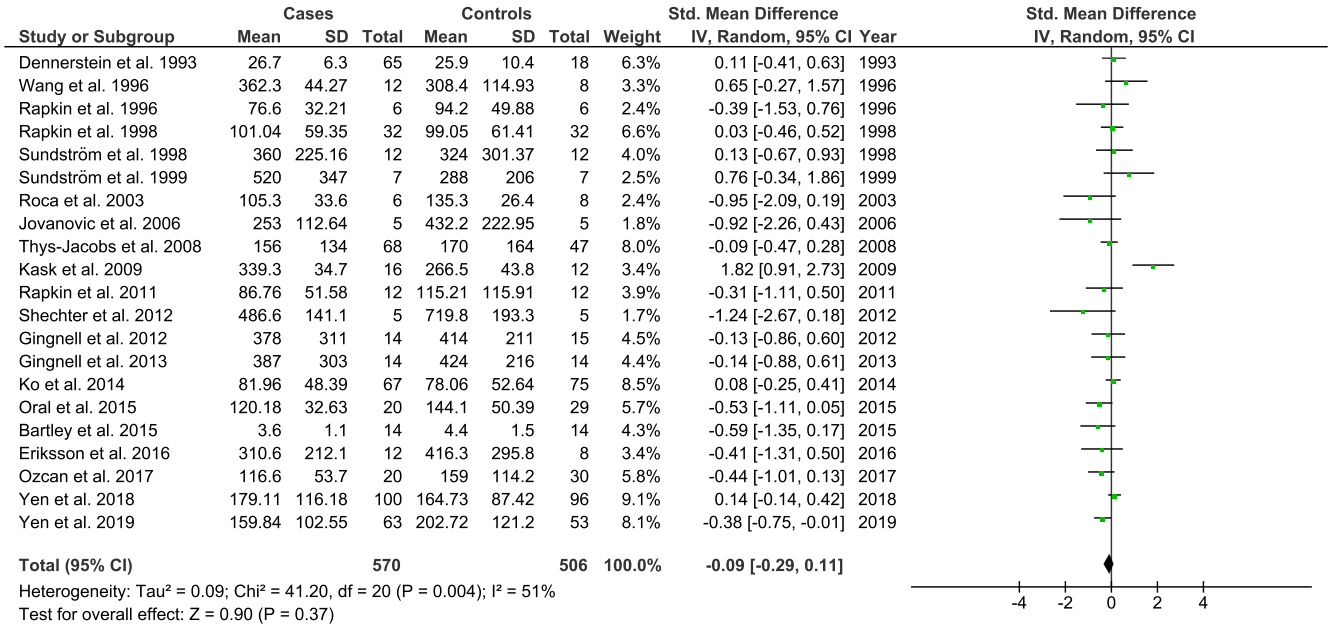

Fig. 3. Forest plot of studies comparing oestradiol in the luteal phase between women with premenstrual dysphoric disorder (PMDD) and healthy controls; negative effect sizes indicate that women with PMDD had lower oestradiol levels than controls.

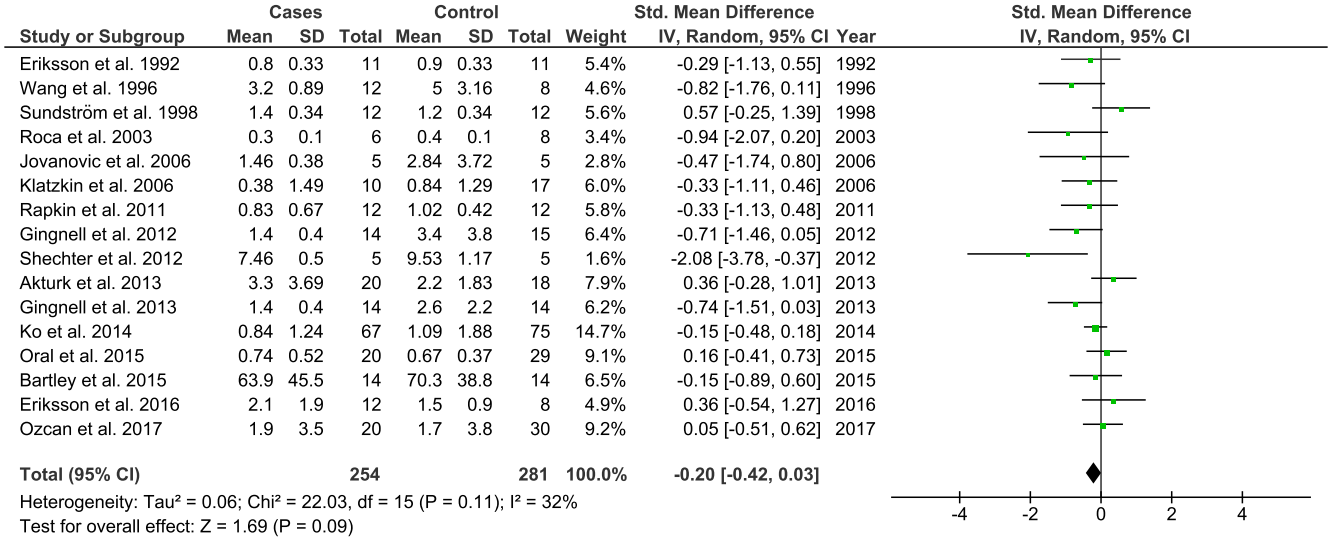

Fig. 4. Forest plot of studies comparing progesterone in the follicular phase between women with premenstrual dysphoric disorder (PMDD) and healthy controls; negative effect sizes indicate that women with PMDD had lower progesterone levels than controls.

95 %CI [−0.70, 0.86]; Z = 0.21, $p = .83$; $I^2 = 38\%$). In the luteal phase, 27 studies were included (Gingnell et al., 2013, 2012; Rapkin et al., 1997, 1998; Jovanovic et al., 2006; Rubinow et al., 1988; Parry et al., 2000; Yen et al., 2019; Wang et al., 1996; Thys-Jacobs et al., 2008; Rapkin et al., 2011; Shechter et al., 2012; Ko et al., 2014; Bartley et al., 2015; Oral et al., 2015; Ozcan et al., 2017; Eriksson et al., 2016; Roca et al., 2003; Sundström et al., 1998, 1999; Cerin et al., 1993; Kask et al., 2009; Rapkin et al., 1996; Akturk et al., 2013; Eriksson et al., 1992; Klatzkin et al., 2006; Girdler et al., 2001). Progesterone did not differ between the two groups in the *meta*-analysis (k = 22; $g = -0.07$, 95 %CI [−0.26, 0.11]; Z = 0.79, $p = .43$; see also Fig. 5), but heterogeneity was significant ($I^2 = 40\%$; $\chi^2 = 34.97$, df = 21, $p = .03$). A subgroup analysis of *late* luteal phase studies did not change the finding, and *meta*-regression identified no effect modifiers.

3.2.2.5. Allopregnanolone. Two studies compared ALLO in the follicular phase (Klatzkin et al., 2006; Timby et al., 2016). *Meta*-analysis suggested higher ALLO in women with PMDD compared to controls (k = 2, $g = 0.97$; 95 %CI [0.47, 1.46]; Z = 3.84, $p = .0001$; $I^2 = 0\%$). In the luteal phase, four studies were included. *Meta*-analysis found no group differences (k = 2; $g = 0.35$, 95 %CI [−0.11, 0.81]; Z = 1.49, $p = .14$; $I^2 = 1\%$).

3.2.2.6. Testosterone. Five studies measured testosterone in the follicular phase (Rubinow et al., 1988; Bartley et al., 2015; Roca et al., 2003; Eriksson et al., 1992; Bloch et al., 1998). *Meta*-analysis yielded an overall *g* of −0.44 (k = 4; 95 %CI [−0.90, 0.03]; Z = 1.85, $p = .06$; $I^2 = 8\%$; $\chi^2 = 3.27$, df = 3; $p = .35$). Three studies examined testosterone in the ovulatory phase (Bartley et al., 2015; Eriksson et al., 1992; Bloch et al., 1998). *Meta*-analysis demonstrated comparable testosterone concentrations between groups (k = 3; $g = -0.80$, 95 %CI [−1.63, 0.02]; Z = 1.91, $p = .06$; $I^2 = 63\%$). Five studies examined testosterone in the

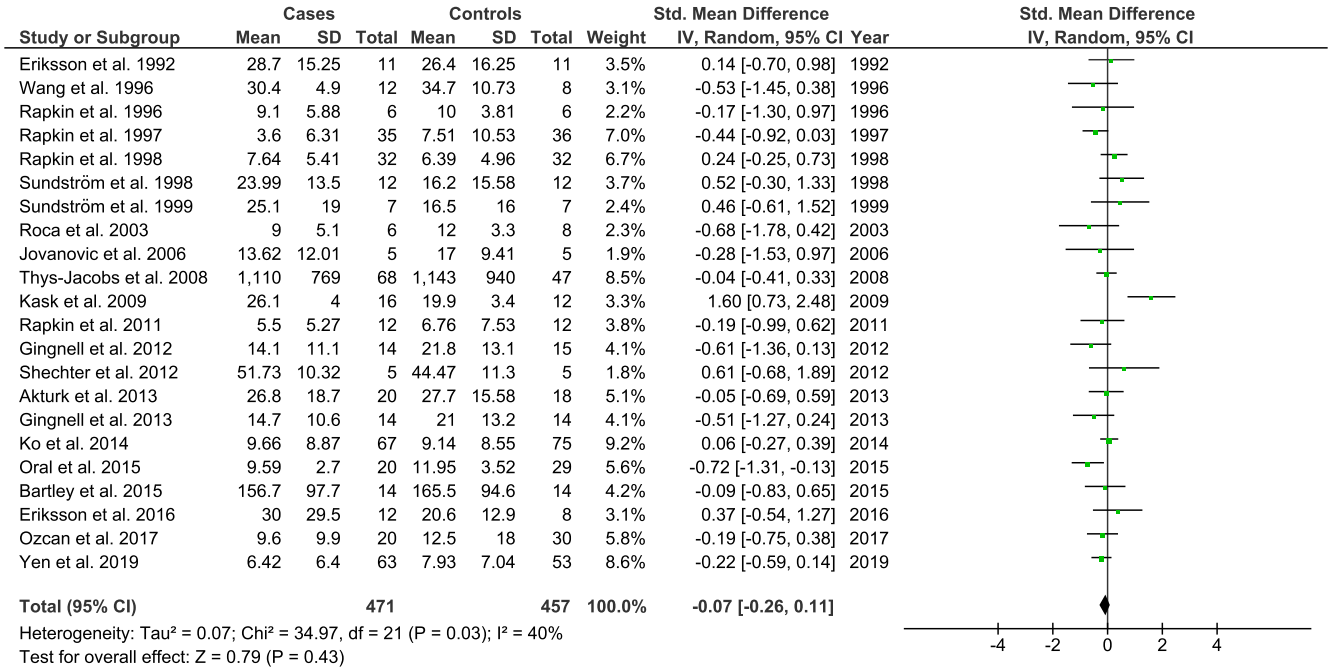

Fig. 5. Forest plot of studies comparing progesterone in the luteal phase between women with premenstrual dysphoric disorder (PMDD) and healthy controls; negative effect sizes indicate that women with PMDD had lower progesterone levels than controls.

luteal phase (Rubinow et al., 1988; Bartley et al., 2015; Roca et al., 2003; Eriksson et al., 1992; Bloch et al., 1998). *Meta*-analysis showed a null-finding (k = 4; $g = -0.20$, 95 %CI [−0.91, 0.51]; Z = 0.54, $p = .59$; $I^2 = 60\%$; $\chi^2 = 7.50$, df = 3; $p = .06$).

3.3. Pregnancy and postpartum depressive disorder

Eight studies compared HPO parameters between women with vs. without a depressive disorder during pregnancy or PPD. For the hormonal studies, the quality score was 4 (see Table 3).

3.3.1. Genetic studies

Two genetic studies compared polymorphisms within *ESR1* and *ESR2* (Pinsonneault et al., 2013; Tan et al., 2018). Pinsonneault et al. (2013) detected that two out of nine investigated polymorphisms within *ESR1* (rs2077647 and TA repeat) were significantly more frequent in women with PPD as compared to healthy controls, but this result did not withstand correction for multiple testing (Pinsonneault et al., 2013). Likewise, Tan and colleagues (2018) found that five polymorphisms within *ESR1* and *ESR2* (*ESR1*: rs2077647, rs2234693, rs9340799, TA repeat; *ESR2*: rs4986938) did not distinguish Chinese women with PPD from healthy controls (Tan et al., 2018).

3.3.2. Hormonal studies

Regarding hormonal studies, Posadas and colleagues (2012) found no differences in oestradiol and progesterone between depressed and non-depressed pregnant women (Posadas et al., 2012). In the postpartum period, Klier et al. (2007) found higher oestrogen levels in patients compared to controls on the third but not the first day after delivery, and no group differences in progesterone levels on either day (Klier et al., 2007). Saleh and colleagues (2013) reported differences between women with PPD and controls regarding oestradiol levels one week after birth, with the former presenting a lower concentration than the latter (Saleh et al., 2013). Also examining women with vs. without PPD one week after birth, Chatzicharalampous and colleagues (2011) found no differences regarding oestradiol, progesterone, and testosterone (Chatzicharalampous et al., 2011). *Meta*-analysis conducted with data within the first week postpartum revealed no differences in oestradiol between cases and controls (k = 2; $g = -0.21$, 95 %CI [−0.92, 0.50]; Z = 0.57, $p = .57$; $I^2 = 78\%$). A study by Harris et al. (1989) conducted 6–8 weeks after birth revealed that oestradiol and progesterone did not differ between depressed and non-depressed women (Harris et al., 1989). In a second study, Harris et al. (1996) examined progesterone at 1, 5 and 35 days after delivery and found no differences between women with PPD and controls (Harris et al., 1996).

3.4. Perimenopausal depressive disorder

Five studies evaluated perimenopausal depressive disorder and HPO-related parameters (see Table 4). The average score from the quality assessments was 4 (Karaoulanis et al., 2014; Flores-Ramos et al., 2014; Schmidt et al., 2002; Hui et al., 2016; Gordon et al., 2016).

3.4.1. Follicle-stimulating hormone

Three studies examined FSH (Karaoulanis et al., 2014; Flores-Ramos et al., 2014; Schmidt et al., 2002). *Meta*-analysis demonstrated comparable levels between cases and controls (k = 2; $g = 0.22$, 95 %CI [−0.13, 0.56]; Z = 1.24, $p = .22$; $I^2 = 0\%$).

3.4.2. Luteinising hormone

Three studies examined LH (Karaoulanis et al., 2014; Flores-Ramos et al., 2014; Schmidt et al., 2002). There were no significant differences between patients and controls (k = 2; $g = 0.18$, 95 %CI [−0.25, 0.61]; Z = 0.81, $p = .42$; $I^2 = 0\%$).

3.4.3. Oestradiol

Regarding oestradiol, Flores-Ramos et al. (2014), Schmidt et al. (2002), Hui et al. (2016) and Karaoulanis et al. (2014) did not report significant differences between depressed and non-depressed perimenopausal women examined at one time point. Gordon et al. (2016) examined perimenopausal fluctuations in oestradiol over four weeks and detected no significant differences across time between individuals with perimenopausal depressive disorder and controls (Gordon et al., 2016). *Meta*-analysis revealed similar oestradiol levels in perimenopausal women with and without depressive disorders (k = 3; $g = -0.13$, 95 %CI [−0.45, 0.20]; Z = 0.77, $p = .44$; $I^2 = 0\%$).

3.4.4. Progesterone

The only study examining progesterone found no significant differences between patients and controls (Flores-Ramos et al., 2014).

3.4.5. Testosterone

Two studies examined testosterone (Flores-Ramos et al., 2014; Schmidt et al., 2002). *Meta*-analysis found no differences between patients and controls (k = 2; $g = -0.17$, 95 %CI [−0.56, 0.21]; Z = 0.88, $p = .38$; $I^2 = 0\%$).

3.5. Depressive disorders unrelated to reproductive transition phases

3.5.1. Genetic studies

Seventeen studies investigated HPO markers in women with depressive disorders unrelated to reproductive transition phases and healthy controls. The average quality score of the hormonal studies was 3.4 (see Table 5).

3.5.2. Hormonal studies

Four genetic studies examined polymorphisms within *ESR1* and *ESR2* (Tsai et al., 2003; Zhang et al., 2017; Ryan et al., 2011; Tiemeier et al., 2005). Tsai et al. found a significant difference in the genotype and allele frequencies of the *ESR1 Pvu*II but not of the *Xba*I polymorphism between depressed Chinese women and healthy controls (Tsai et al., 2003). By contrast, Tiemeier et al. found no significant difference in a related haplotype between Caucasian depressed women and controls (Tiemeier et al., 2005). Zhang et al. reported a statistically significant difference in the genotype and allele distributions of an *ESR2* SNP (rs1256049) between Chinese women with major depressive disorder and healthy controls (Zhang et al., 2017). However, a second *ESR2* SNP (rs4986938) did not differ between depressed and non-depressed women. Finally, Findikli et al. reported that women with depressive disorders had a higher G protein-coupled oestrogen receptor 1 (GPER) level than controls (Findikli et al., 2017).

3.5.2.1. Follicle-stimulating hormone. Six studies examined FSH (Amsterdam et al., 1981; Winokur et al., 1982; Amsterdam et al., 1983; Antonijevic et al., 2003; Young et al., 2000; Rajewska and Rybakowski, 2003). *Meta*-analysis found comparable FSH levels between depressed and non-depressed women (k = 2; $g = -1.62$, 95 %CI [−3.37, 0.13]; Z = 1.82, $p = .07$; $I^2 = 92\%$). A subgroup analysis by menopausal status did not alter the null-finding.

3.5.2.2. Luteinising hormone. Only one out of five studies identified a difference in LH between depressed and non-depressed women, with depressed women demonstrating significantly lower levels than controls (Amsterdam et al., 1981; Winokur et al., 1982; Amsterdam et al., 1983; Antonijevic et al., 2003; Young et al., 2000). These studies could not be *meta*-analysed due to a lack of available data.

3.5.2.3. Oestradiol. Seven studies examined oestradiol in women with and without depressive disorders (Amsterdam et al., 1981, 1983; Antonijevic et al., 2003; Young et al., 2000; Rajewska and Rybakowski, 2003; Erdinçler et al., 2004; Findikli et al., 2017). *Meta*-analysis did not reveal any group differences (k = 4; $g = -0.22$; 95 %CI [−0.50, 0.05]; Z = 1.59, $p = .11$; $I^2 = 0\%$). A subgroup analysis by menopausal status did not alter the null-finding.

3.5.2.4. Progesterone. Two studies assessed progesterone (Young et al., 2000; Erdinçler et al., 2004). *Meta*-analysis found no group differences (k = 2; $g = -0.93$; 95 %CI [−1.93, 0.07]; Z = 1.83, $p = .07$; $I^2 = 85\%$).

3.5.2.5. Testosterone. Six studies investigated testosterone (Amsterdam et al., 1981, 1983; Antonijevic et al., 2003; Young et al., 2000; Rajewska and Rybakowski, 2003; Erdinçler et al., 2004; Findikli et al., 2017). *Meta*-analysis revealed that depressed women presented with lower testosterone levels than healthy controls (k = 5; $g = -0.58$; 95 %CI [−0.93, −0.22]; Z = 3.19, $p = .001$; see also Fig. 6). The heterogeneity was significant ($I^2 = 72\%$; $\chi^2 = 14.43$, df = 4, $p = .006$). Subgroup analysis indicated that studies standardizing sampling regarding time of day were more likely to find lower testosterone in patients versus controls (k = 5; $g = -0.58$; 95 %CI [−0.93, −0.22]; $\chi^2 = 4.20$, df = 1, $p = .04$). A subgroup analysis by menopausal status did not alter this finding.

3.5.2.6. DHEA and DHEA-S. Two studies analysed DHEA (Jiang et al., 2017; Poór et al., 2004). These concentrations did not differ between depressed and non-depressed women (k = 2; $g = 0.00$; 95 %CI [−0.37, 0.38], Z = 0.01, $p = .99$; $I^2 = 0\%$). Four studies investigated DHEA-S (Erdinçler et al., 2004; Markianos et al., 2007; Oulis et al., 2014; Jiang et al., 2017). The *meta*-analysis revealed comparable levels between groups (k = 4; $g = -0.30$, 95 %CI [−0.69, 0.08]; Z = 1.55, $p = .12$; see also Fig. 7). However, there was significant heterogeneity ($I^2 = 71\%$; $\chi^2 = 10.32$, df = 3; $p = .02$). Subgroup analyses indicated that studies using plasma compared to saliva found lower DHEA-S in women with depressive disorders versus healthy controls (k = 4; $g = -0.30$, 95 %CI [−0.69, 0.08]; Z = 1.55, $p = .12$; $\chi^2 = 5.57$, df = 1, $p = .02$). A subgroup analysis by menopausal status did not alter this finding.

4. Discussion

We report three main findings: First, studies of higher methodological quality found lower luteal oestradiol in women with PMDD. Second, there was little evidence for alterations in hormones of the HPO-axis in women with pregnancy, postpartum, or perimenopausal depressive disorders. Lastly, studies of higher methodological quality found that women with depressive disorders unrelated to reproductive transition phases had comparably lower testosterone and DHEA-S levels than healthy controls (a summary of all results can be found in Table 6).

The first finding suggests that study quality is crucial in research on PMDD, a notion that was recently highlighted in an article summarising methodological recommendations for research devoted to menstrual cycle phenomena (Schmalenberger et al., 2021). The emerging role of oestrogen signalling in premenstrual symptom manifestation warrants further research into polymorphisms and DNA methylation within oestrogen receptor encoding genes in this population, which may underlie some of the observed alterations.

The second finding is more complex. Only one study compared depressed and non-depressed pregnant women during pregnancy, reporting a null-finding. This finding is in line with early evidence suggesting no significant differences in plasma oestrogen levels in these same groups (Mehta et al., 2014). By contrast, several studies investigated women with PPD, mostly with negative findings, although one study reported lower oestradiol in women with PPD one week after postpartum. Interestingly, studies assessing hormones in relation to postpartum dysphoria ("baby blues") have shown higher levels of oestradiol in affected women (Heidrich et al., 1994; O'Hara et al., 1991). This suggests that any potential hormonal contributions to mood symptoms in postpartum are highly time-sensitive. In addition, genetic studies seem to support a role for *ESR1* in the aetiology of PPD, corroborating similar findings by others who reported four SNPs in the fourth and fifth introns of *ESR1* to significantly associate with PPD (Costas et al., 2010). By contrast, the finding that women with and without perimenopausal depressive disorder did not differ in HPO-axis parameters is in line with most longitudinal studies on hormonal variability and perimenopausal depressive symptoms (Avis et al., 2001; Woods et al., 2008).

The third finding is of lower testosterone and DHEA-S levels in women with depressive disorders compared to healthy controls. This finding is in line with a recent *meta*-analysis, which found lower testosterone in men with depressive disorders as compared to healthy

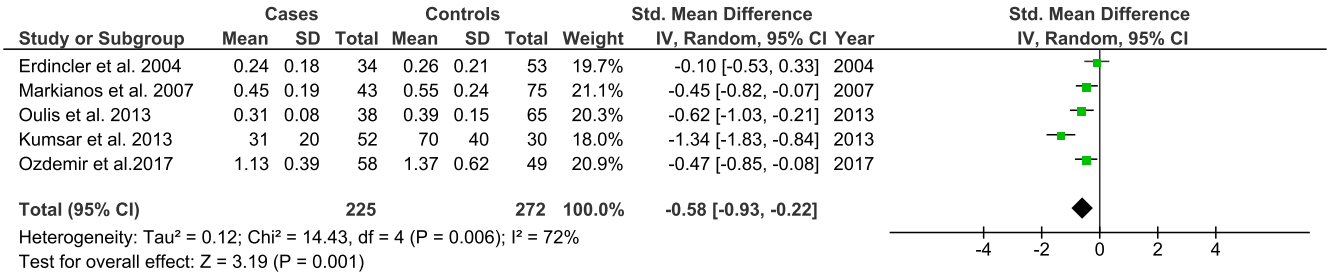

Fig. 6. Forest plot of studies comparing testosterone between women with depressive disorders unrelated to reproductive transition phases and healthy controls; negative effect sizes indicate that women with depressive disorders had lower testosterone levels than controls.

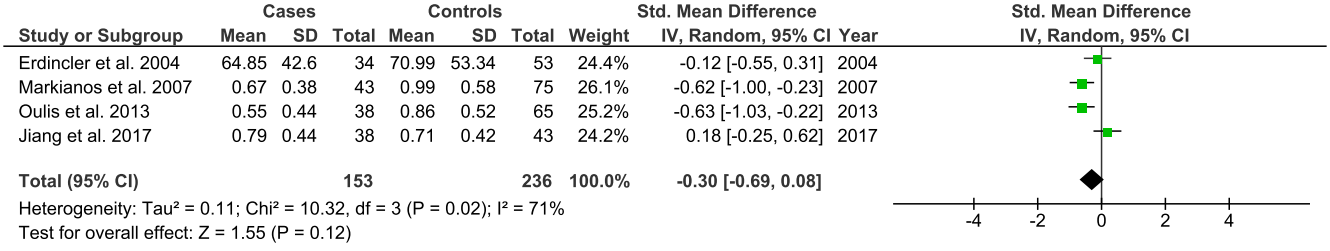

Fig. 7. Forest plot of studies comparing DHEA-S between women with depressive disorders unrelated to reproductive transition phases and healthy controls; negative effect sizes indicate that women with depressive disorders had lower DHEA-S levels than controls.

Table 6
Summary of results.

Variables	*ESR1*	*ESR2*	GPER	FSH	LH	E_2	P_4	ALLO	T	DHEA	DHEA-S
Premenstrual dysphoric disorder	*	Ø									
Follicular phase				–	Ø	Ø	Ø	*	Ø	–	–
Ovulation phase				–	–	Ø	Ø	–	Ø	–	–
Luteal phase				Ø	Ø	*	Ø	Ø	Ø	–	–
Pregnancy depressive disorder	–	–	–	–	–	Ø	Ø	–	–	–	–
Postpartum depressive disorder	Ø	Ø	–	–	–	¥	Ø	–	Ø	–	–
Perimenopausal depressive disorder	–	–	–	Ø	Ø	Ø	Ø	–	Ø	–	–
Depressive disorders unrelated to reproductive transition phases	¥	*	*	Ø	¥	Ø	Ø	–	*	Ø	*

Note: * findings support a relationship between the gene/hormone and the specific mood disorder; Ø findings are non-supportive of a relationship between the gene/hormone and the specific mood disorder; ¥ findings are unclear; *ESR1* = gene encoding the oestrogen receptor alpha, *ESR2* = gene encoding the oestrogen receptor beta, FSH = follicle-stimulating hormone, GPER = G protein-coupled oestrogen receptor 1, LH = luteinising hormone, E_2 = oestradiol , P_4 = progesterone, T = testosterone, ALLO = allopregnanolone, DHEA = dehydroepiandrosterone, DHEA-S = dehydroepiandrosterone sulfate.

controls (Fischer et al., 2019). As with PMDD, the testosterone finding was dependent on standardised morning sampling. This concurs with endocrinological guidelines suggesting that due to natural diurnal variation in testosterone levels, samples should be collected in the morning (Bhasin et al., 2010). Similarly, DHEA-S levels were lower in women suffering from depressive disorders, but only in studies taking plasma samples. Importantly, in the same studies, the participants' age was comparably higher, which might have significantly contributed to the observed findings. Morrison and colleagues (Morrison et al., 2001) examined hormonal variation and depression in women aged 35–47 and concluded that higher DHEA-S levels were associated with depressive symptoms in younger women, whereas lower levels were associated with depressive symptoms in older women. However, we could not confirm this finding in our sample. Presently, the data is inconclusive regarding an involvement of polymorphisms within *ESR1* and *ESR2* in depressive disorders. Considering the scarce literature on this topic, further investigation is needed.

Our study is the first systematic summary of the literature on HPO functioning in female mood disorders. The strict inclusion criteria in terms of diagnosis, potential confounders, and study design enhances the reliability of our findings and *meta*-regression and subgroup analyses allowed us to identify methodological factors that need to be considered by future research. However, caution must be exercised in interpreting the findings regarding certain parameters (e.g., ALLO) due to the low numbers of available studies. Additionally, even after contacting the authors, it was not possible to access a number of older datasets. Nevertheless, these results were included in the systematic review and showed an almost 100% overlap with the findings of the *meta*-analyses. The risk of bias assessment identified a number of methodological problems. However, our quality rating was rather conservative (e.g., nearly all studies lost 2 out of 10 points due to a failure to report blinding procedures) and *meta*-regression/subgroup analyses enabled us to identify particularly relevant factors that should be considered by future research. Finally, it is important to highlight that although absolute hormonal values seemed to have a small impact on the development of female depressive disorders, fluctuations in sex hormones have repeatedly been hypothesised to alter neurochemical pathways linked to depression (Soares and Zitek, 2008; Bloch et al., 2000; Schmidt et al., 1998; Willi et al., 2021). Building on empirical findings of links between hormonal fluctuations and depressive symptoms (Mehta et al., 2014; Lee et al., 2015; Guintivano et al., 2014; Schmidt et al., 2015), it seems possible that there is a subgroup of women who are more prone to display reproductive phase transition mood disorders due to an increased sensitivity to such variation.

5. Conclusions

In sum, we believe it is important for PMDD researchers to continue to adhere to highly standardised sampling schedules, and in so doing to assess how hormonal fluctuations contribute to symptoms across the menstrual cycle. In pregnancy, postpartum and perimenopausal depression, the magnitude of hormonal increases and decreases may render it more difficult to unravel the role of sex hormones in depressive episodes. Large-scale longitudinal studies will be crucial to help to detect windows of vulnerability. Finally, future studies in depressive disorders unrelated to reproductive transition phases should attempt to establish whether low testosterone/DHEA-S are antecedents or consequences of depressive symptoms. A better understanding of female biological changes during different reproductive phases may contribute to effective treatment options and reduce disease burden.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yfrne.2021.100929.

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